REMARKS

In the Office Action dated January 15, 2004, claims 18-19 are pending and are under consideration. Claims 18-19 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Green et al. (The Veterinary Record, May 2, 1987) and Geresi et al. (Ann. Immuno. Hung 25:37-40, 1985) in view of Wu et al. (J. Immunol. 148:1519-1525, 1992) and Gluck et al. (U.S. Patent No. 5,879,685). Claim 18 is also rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

This Response addresses each of the Examiner's rejections. Accordingly, the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Applicants, through the undersigned, wish to thank Examiner Shahnan-Shah and Primary Examiner Swartz for the courtesy and assistance extended on behalf of the Applicants during a telephone interview conducted with the undersigned on April 20, 2004.

Claims 18-19 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Green et al. and Geresi et al. in view of Wu et al. and Gluck et al. Claims 18-19 are directed to a multicomponent clostridial vaccine composition comprising at least two species or serotypes of Clostridium, a retroviral antigen and a saponin adjuvant.

The Examiner contends that Green et al. teach a formulation of a multivalent clostridial vaccine for the purpose of stimulating a protective immune response against multiple strains and species of Clostridia. The Examiner admits that Green et al. fail to teach the use of a viral antigen in the multivalent clostridial vaccine. The Examiner also acknowledges that the vaccine disclosed by Green et al. employs aluminum hydroxide as the adjuvant.

The Examiner also contends that Geresi et al. teach a vaccine composition containing multicomponent clostridial species and a viral immuogen. The Examiner admits that Geresi et al. fail to teach the use of a saponin adjuvant.

Furthermore, the Examiner contends that Wu et al. disclose that the use of a saponin adjuvant in association with a viral antigen. According to the Examiner, Wu et al. teach that vaccine formulations containing the saponin adjuvant produced significantly higher titers of antibody than alum absorbed vaccines.

Regarding Gluck et al., the Examiner contends that this reference teaches an immunostimulating combination of influenza virus and *Clostridium tetani*.

In the Examiner's opinion, it would have been *prima facie* obvious to one skilled in the art, at the time the invention was made, to modify or combine the compositions of Green et al. and Geresi et al. by including a respiratory virus taught by Gluck et al. and the saponin adjuvant taught by Wu et al., allegedly because all of the references are directed to the formulation of vaccines for enhanced immune response. The Examiner contends that those skilled in the art would have been motivated to combine these compositions because Green et al. and Gluck et al. both employ formulations of multicomponent clostridial vaccines and because "Wu et al. teach the use of saponin as an adjuvant which provides for an enhanced immune response when in association with either a clostridial antigen or a viral antigen, respectively." See, Page 4, lines 13-15 of the Office Action. The Examiner also alleges that use of different adjuvants in vaccines, e.g., saponin, is well known in the art and saponin adjuvant has been commercially available (e.g., Quil A). Therefore, the Examiner concludes that, in the absence of unexpected results, Green et al. and Geresi et al., in view of Gluck et al. and Wu et al., render the instantly claimed vaccines obvious.

In the first instance, Applicants respectfully submit that the Examiner's allegation that Wu et al. teach the use of saponin as an adjuvant for use in association with either a clostridial antigen or a viral antigen, respectively, is unfounded. Wu et al. only examined the effect of including saponin in alum-adjuvanted vaccine compositions containing an HIV envelope protein. Wu does not teach or even suggest making vaccine formulations containing a clostridial antigen.

In fact, Applicants respectfully submit that prior to the present invention, there was no recognition in the art that a water-soluble adjuvant such as saponin could be used as an adjuvant to enhance the immunogenicity of a clostridial antigen. Prior to the present invention, it was generally recognized that clostridial toxoids were soluble proteins of relatively low antigenicity and poor stability; and thus, clostridial vaccines required adjuvants, typically, aluminum compounds, in order to increase antigenic potency and to enhance stability. Aluminum compounds were capable of adsorbing and/or precipitating clostridial toxoids, as well as retaining the toxoids at the injection site. However, as described in the specification at page 1, lines 35-37, aluminum compound-based adjuvants often provoked severe persistent local reactions, such as granulomas, abscesses and scarring, when injected subcutaneously or intramuscularly.

The present inventors have uniquely recognized that stable, potent, multicomponent clostridial vaccines can be made with a rapidly dispersed, soluble adjuvant, such as a saponin, without the use of a depot adjuvant such as an aluminum compound.

While saponins may have been used as an adjuvant in association with other antigens, Applicants respectfully submit that there was nothing in the prior art that would have motivated those skilled in the art to use a saponin, absent any depot adjuvant, in order to produce effective clostridial vaccines. Furthermore, Applicants respectfully submit that those skilled in the art

would not have had a reasonable expectation that a saponin, absent any depot adjuvant, would be effective as an adjuvant in clostridial vaccines.

In this connection, Applicants respectfully direct the Examiner's attention to the cited reference, Wu et al., which clearly showed that a saponin adjuvant, when used alone without alum, did not have any adjuvant effect. Specifically, in Figure 2 at page 1521, Wu et al. demonstrated that the immunostimulating effect of the saponin adjuvant, QS-21, was observed only when the saponin was used in combination with alum, not when used alone. Therefore, Applicants respectfully submit that Wu et al. would not have provided any motivation to those skilled in the art to make a vaccine composition with a saponin adjuvant without an aluminium compound. Moreover, Wu et al. clearly taught away from the presently claimed invention.

Applicants further respectfully submit that none of the remaining references provide any suggestion or motivation to those skilled in the art to combine the respective teachings of each other. Applicants submit that Green et al. teach a vaccine composition which includes an aluminum hydroxide adjuvant, which is specifically described in the present application as unsuitable for clostridial vaccine compositions. Thus, Green et al. provide a clear teaching away from the composition of the present invention.

As to Geresi et al., this reference fails to teach the use of any adjuvant, let alone a soluble adjuvant such as a saponin.

Gluck et al. may have taught a combination of influenza virus and *Clostridium tetani*. However, Applicants respectfully submit that Gluck et al. do not teach or even suggest the use of saponin as an adjuvant in the vaccine disclosed therein.

Clearly, none of the cited references, taken alone or in combination, provide any teaching or suggestion that would have motivated those skilled in the art to combine the

respective teachings of the references in order to arrive at the presently claimed vaccine compositions.

Furthermore, Applicants respectfully submit that the results achieved with the presently claimed vaccine compositions are unexpected. In particular, those skilled in the art would not have reasonably expected that the use of soluble adjuvants that are readily dispersed from the injection site and have no depot effect, such as saponin, in a multicomponent clostridial vaccine, would be successful in enhancing the potency of clostridial antigens.

In this regard, Applicants respectfully direct the Examiner's attention to the specification, at pages 13-18, where multicomponent clostridial vaccines containing a saponin adjuvant were compared to vaccines containing the same clostridial components but with aluminium hybroxide gel as adjuvant. As described at pages 14-15, while the $Al(OH)_3$ gel-adjuvanted vaccines provoked chronic local reactions (such as swelling) for an extended period (e.g., 6 weeks), the saponin-adjuvanted vaccine only induced transient reactions at the injection sites that disappeared quickly after a few days. In addition, a saponin-adjuvanted vaccine containing seven clostridial antigens induced stronger antibody response against *C. chauvoei* than a vaccine containing the same clostridial antigens and aluminium hydroxide gel as adjuvant.

Accordingly, Applicants respectfully submit that there is no suggestion in the cited references to combine the separate features of Green et al., Geresi et al., Wu et al. or Gluck et al. in order to achieve the claimed invention. In addition, even assuming, *pro arguendo*, that there was a suggestion to combine the respective teachings of the cited references, the results achieved by the claimed vaccines are still unexpected. Therefore, Applicants respectfully submit that the rejection of claims 18-19 under 35 U.S.C. §103(a) is overcome and withdrawal thereof is respectfully requested.

Claim 18 is rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner contends that the recitation "wherein said vaccine composition does not contain an aluminum compound-based depot adjuvant" is not supported by the original disclosure.

Applicants respectfully disagree with the Examiner. Support for the recitation "wherein said vaccine composition does not contain an aluminum compound-based depot adjuvant" is found throughout the specification as originally filed. For example, the specification at page 1, lines 14-15, refers to "multicomponent clostridial vaccines made without stabilizing carriers or depot adjuvants". The specification also describes:

> "[A]luminum compounds are used as adjuvants, which are capable of adsorbing and/or precipitating clostridial toxoids, as well as retaining the toxoids at the injection site, are typically used. ..... Other potent depot adjuvants, such as water-in-oil emulsions and carbopol, have also been used in clostridial vaccines."

See, Page 1, line 35 to page 2, line 2 of the specification. In addition, the specification states:

> "Central to the present invention is the surprising discovery that stable, potent, multicomponent clostridial vaccines can be made without the use of depot adjuvants. In particular, the present invention provides for vaccines including rapidly dispersed, soluble adjuvants, that is, adjuvants that are nto retained at the injection site for a significant period of time, thereby exhibiting low tissue reactivity."

See, Page 4, lines 24-26 of the specification.

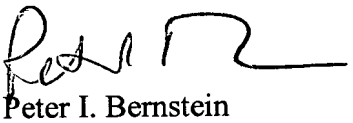
Therefore, Applicants respectfully submit that vaccine compositions characterized by the absence of an aluminum compound-based depot adjuvant are adequately supported by the specification as originally filed in a manner that fully complies with the written description

requirement under 35 U.S.C. §112, first paragraph. Accordingly, withdrawal of the rejection of claim 18 under 35 U.S.C. §112, first paragraph is respectfully requested.

Applicants have also added claim 20, drawn to a vaccine composition comprising (i) immunogens from at least two species or serotypes of Clostridium; (ii) an antigen from a respiratory virus; and (iii) an adjuvant consisting essentially of a saponin. Applicants respectfully submit that similar to claim 18, claim 20 is adequately supported by the specification as originally filed. No new matter is introduced.

In view of the foregoing amendments and remarks, it is respectfully submitted that the application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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